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Low-dose intravenous immunoglobulin (IVIg) in different immune-mediated conditions

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ABSTRACT

IVIg has been used for a long time as a replacement therapy for primary and secondary immunodeficiencies. Beside this supplementary role, when used at higher doses (i.e., 2 g/kg/monthly) it exerts an immunomodulatory role able to control multiple autoimmune and systemic inflammatory diseases. Several mechanisms of action have been described and hypothesized, nonetheless a synergistic action on the different component of the immune response seems to be crucial.

The other side of the coin are the costs which showed an increase during the years due to the production of highly purified preparations which limit side reactions. This renders the product not easily accessible especially for low-income countries. Moreover, it is based on plasma donations that experienced a significant shrinkage after the COVID-19 pandemic and the consequences are still impactful.

Due to the above-mentioned problems different authors tried to find out if a lower dosage of IVIg (< 2 g/kg/monthly) might exert an immunoregulatory role. In this review we aimed to summarize the current literature about a possible beneficial effect of a lower dosage of IVIg in multiple conditions that would help to treat a vast majority of patients. Even though in some cases (e.g., Kawasaki disease and immune thrombocytopenia) results are promising, for other conditions more research is needed.

1. Introduction

Intravenous immunoglobulin (IVIg) has been historically used as a replacement therapy in primary and secondary immunodeficiencies. In addition to its role in protecting against infections in immunodeficiencies, IVIg interacts with adaptive and innate immune system fulfilling an immunomodulatory role [1]. Over the years the use of IVIg was extended as immunomodulatory therapies in different immune-mediated disorders [2]. In the last 25 years, IVIg has had a breakthrough impact in the treatment of autoimmune disorders, above all neurological [3–5]. In adults, the immunomodulating action is achieved by a high-dose protocol (2 g/kg) divided into 2 to 5 days per month, while for pediatric subjects it is IVIg 2 g/Kg (max 80 g) in single administration or divided into 2 doses in selected cases.

Plasma-derived human immunoglobulin products are a pooled preparation of polyclonal immunoglobulin obtained from plasma of several thousand healthy donors. The IVIg contains >95% IgG, <2.5% IgA, and negligible amount of IgM. Among the IgG subclasses, IgG1 varies from 55 to 70%, IgG2 from 0 to 6%, and IgG4 from 0.7 to 2.6%, according to the size and composition of the donor pools used in various proprietary IVIg preparations. The product is purified by enzymatic treatment at low pH, followed by fractionation and chromatography. Treatment with solvent detergents at low pH, virus filtration, or the addition of caprylate, are additional powerful measures to filter out viruses and to reduce the probability of transmitting prions [6,7].

Approved autoimmune indications for high-dose IVIg therapy

Abbreviations: DM, Dermatomyositis; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; KD, Kawasaki diseases; SCIg, subcutaneous immunoglobulin.

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include immune thrombocytopenia (ITP), Kawasaki disease (KD), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Guillain–Barré syndrome (GBS) [8–10]. However, randomized clinical trials have shown the efficacy of IVIg in other autoimmune and inflammatory diseases such as anti-neutrophil cytoplasm antibody-associated systemic vasculitis, autoimmune hemolytic anemia, myasthenia gravis, graft-versus-host disease, inflammatory myopathies, stiff-person syndrome, neuromyelitis spectrum disorders, or autoimmune encephalitis [5,11–13].

In antibody deficiencies, intravenous immunoglobulin replacement therapy is given at an incremental dose adjusted to the individual patient and to his tolerability. A low-dose protocol, 0.3–0.6 g/kg once monthly is the standard dosage in replacement therapy. When administered in the setting of hypogammaglobulinemia, antibody deficiency disorders, and/or other immunodeficiency states, IVIg offers a passive immunity providing an adequate concentration of antibodies against a broad spectrum of pathogens.

Patients with autoimmune/inflammatory conditions usually require intravenous administration of high doses IVIg reaching 2500 to 3500 mg per deciliter. In these high-dose protocols, IVIg has several potential anti-inflammatory and immunomodulatory effects. [14]. Considering all the different pathophysiological mechanism and the various modalities of action of immunoglobulin, it is not surprising that IVIg can positively influence the outcome of several immune-mediated diseases. Different theories have been proposed to clarify the mechanisms including the interaction with Fc receptors on phagocytic cells in the spleen and liver such as splenic macrophages [15,16]; inhibition of dendritic cell differentiation and maturation [14]; reduction of proinflammatory subsets of peripheral blood monocytes (CD14 + CD16++) and suppression of cytokine production by these cells; suppression or neutralization of cytokines by specific antibodies on the IVIg [17]; block of leukocyte adhesion molecule binding to the vascular endothelium; interfering the Fas ligand-mediated apoptosis by anti-Fas antibodies in the IVIg; induction of inhibitory Fc-gamma-RIIB receptors on effector macrophages; supply of anti-idiotypic antibodies directed against idiotypes on circulating autoantibodies (anti-idiotypic antibodies in the IVIg may bind either to circulating autoantibodies, resulting in increased clearance, or to B cell immunoglobulin receptors, leading to downregulation of antibody production) [14]; provision of neutralizing antibodies to microbial toxins. However, have also been hypothesized effects on the complement system, such as solubilization and clearance of immune complex deposits and/or inhibition of the binding of active complement components to target tissues [18]. Thus, IVIg can directly influence the functions of innate and adaptive immune system's cells such as T and B cells, macrophages, and dendritic cells [15,19] (Table 1). Probably, more than one mechanism contributes to the immune modulation in autoimmune disease [8].

Several studies support the anti-inflammatory and immunomodulatory action of high-dose IVIg claiming to the increased IgG catabolism due to the saturation of the protective transport receptors FcRn highly expressed on many tissues as well as on vascular endothelial cells [9] (Table 1). Normally, IgG antibodies bind to FcRn to return via endocytotic vesicles intact back into the circulation, being protected from degradation by the lysosomes [20]. The supraphysiological levels of IgG, derived from IVIg administrations, saturate the FcRn, so a portion of endogenously produced pathogenic IgG antibodies are not recycled back to the circulation but degraded. As a result, the infused IVIg, by competing with pathogenic autoantibodies for FcRn binding, reduces the serum half-life of autoantibodies by approximately 40% causing a reduction of circulating IgG autoantibodies [8].

However, although the therapeutic value of human IgG is evident, the mechanisms involved are not entirely understood, especially in immunomodulation in autoimmune diseases. This, as well as regulatory and policy issues, has led to differentiation of the indications into those approved by the European Medicines Agency (on-label) and those used off-label. This categorization varies greatly across European countries, leading to different standards care and treatment protocols. Additionally, the COVID-19 pandemic has led to an interruption of plasma collecting and consequently to a shortage of plasma-derived products (incl. IgG). In most European countries, limited availability of this products has triggered further restrictions on IgG use via prioritization of specific patient subpopulations [21].

Table 1
Anti-inflammatory and Immunomodulatory activities of Intravenous Immunoglobulin (IVIg). DC denotes dendritic cells, FcγR receptor for the Fc portion of IgG, FcRn neonatal Fc receptor, GR glucocorticoid receptor.

Fab-dependent activities	Fc-dependent activities
Interference with idiotypic/anti-idiotypic network	Inhibition of phagocytosis
Antibodies to immunomodulatory proteins	Blockade of immune-complex access to FcγR
Antibodies to superantigens and pathogens	Binding to activating and inhibitory FcγR
Block of leukocyte adhesion molecules	Alterations in GR binding affinity
Natural antibodies	Regulation of DC maturation and function
Antibodies against cytokines and/or chemokines	Inhibition of antibody-dependent cellular toxicity
Neutralization of pro-inflammatory cytokines	Modulation of antibody half-life through FcRn
Blocking of activated complement components	Inhibition of deposition of activated complement component on target tissues
Neutralization of autoantibodies	Increase of inhibitory FcγRIIb expression
Modulation of antibody production	Immunomodulatory effects of sialylated IgG
Regulation of DC maturation and function	Increase of Treg cell

In literature there are numerous scientific evidence regarding the efficacy of high-dose immunoglobulin in immune-mediated diseases. On the other hand, few studies support the efficacy of lower doses, such as medium-high doses (0.8–1 g/kg) or low-dose (0.4–0.6 g/kg), for acute or maintenance treatment in inflammatory/autoimmune disorders [22].

Considering that IVIg production depends on a broad donor's pool and the therapy often requires large doses (up to 2 g/kg body weight), the difficulties and the concerns regarding its availability might be challenging and pose logistical and financial burdens for patients. To address these limitations and to optimize IVIg therapy, several strategies could be considered. Firstly, research and clinical trials should be conducted to determine the minimum effective dosage of IVIg for various immune conditions with a consequent reduction of the minimum effective dosage. Finding the lowest effective dose could help to cut-down the overall amount of product needed for treatment, potentially making the treatment more accessible to patients. Secondly, it is important to optimize dosage based on ideal weight, instead of using the real weight of the patient which may include excess fluid or adipose tissue [23]. Furthermore, this approach ensures that the dosage is more tailored to the patient's specific needs. Thirdly, the length of the interval between doses must be considered. As the patient's condition stabilizes, the interval between IVIg treatments should be gradually extended [5]. However, for patients who require IVIg therapy on a long-term basis, regular reassessment of their clinical manifestations is essential. This evaluation allows to determine the progressive necessity of IVIg treatment and whether any adjustments in dosage or interval are appropriate based on the patient's response and disease progression [5]. Additionally, ongoing research and advancements in immunoglobulin therapy may lead to more refined and efficient treatment approaches in the future. In support of what has been said so far, this review aims to investigate whether a reduced dosage of intravenous immunoglobulins has the same efficacy as high dosage and whether it can be considered a valid option for immune-mediate diseases.

2. Low-dose IVIg in immune-mediated diseases

2.1. Kawasaki disease

Kawasaki disease (previously known as mucocutaneous lymph node syndrome) is a vasculitis that usually affects infants or young children. The diagnosis is based upon evidence of systemic inflammation (fever) in association with signs of mucocutaneous inflammation that typically develop after brief nonspecific symptoms of respiratory or gastrointestinal tract [24]. Since it affects medium size vessels, coronary artery lesions, dilatation, or aneurysm formation are the most common complications that typically occur in those patients that do not receive a prompt therapy. The pathogenesis is still unknown; however, the leading theory is the presence of a stimulus that triggers an immune-mediated inflammatory cascade in genetically predisposed children [25].

The standard initial therapy for Kawasaki disease is represented by a single infusion of high-dose IVIg (2 g/kg once) together with aspirin. This approach showed to lower the incidence of coronary artery lesions and to shorter the duration of fever without extra adverse events as compared to the former four-day regimen (400 mg/kg/day for four consecutive days) [26]. A Japanese randomized prospective study of 2007 did not find any statistically significant difference concerning the incidence of coronary aneurysms between patients receiving a single IVIg dose of 2 g/kg or a single dose of 1 g/kg [27]. However, this study could not be conclusive due to the small number of participants and the differences in treating patients resistant to the initial IVIg dose [27]. A later study found that that a medium-high dose (1 g/kg) IVIg was effective in the majority (80%) of Kawasaki patients [28]. Matsuura et al. [29] suggested a new scoring system (Less high-risk score) that, together with the known Kobayashi score, allowed identifying a low-risk population of Kawasaki disease which was supposed to respond efficiently to 1 g/kg IVIg. Recently, an open-label, multicenter three-arm randomized controlled clinical trial compared the efficacy of three different IVIg regimens as initial therapy for Kawasaki disease: 2 g/kg per day once, 1 g/kg per day for two consecutive days, and 1 g/kg per day once. Considering the fever duration, the occurrences of coronary artery lesions, the changes in laboratory tests, adverse events, and hospital stay, this study highlighted that a single dose of 1 g/kg IVIg could be an effective and low-cost initial therapy for Kawasaki patients since it reduced the total dose of IVIg [26].

As previously stated, Kawasaki disease mainly occurs in infants and the proportion of patients over 6 years old is about 8%. Older children are heavier, consequently the total amount of IVIg is higher and the medical costs increase. Suzuki et al. [30] investigated whether the outcomes were different between an initial dose of 2 g/kg IVIg and 1 g/kg IVIg in Kawasaki children with a weight of 25 kg or more. Authors did not report any significant difference in the proportion of coronary artery abnormalities, IVIg resistance, hospital stay, or adverse effects. Only medical costs were higher in the high-dose group [30].

2.2. Immune thrombocytopenia

In 1980 Paul Imbach was caring for a child with refractory immune thrombocytopenia (ITP), bleeding and secondary hypogammaglobulinemia who received IVIg. Imbach observed a dramatic increase of his platelet count, supposing that IVIg might modulate the immune response in multiple synergistic ways acting on different components of the immune system [31].

ITP (also called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura) is a disorder characterized by thrombocytopenia that may affect subjects of all ages, with peaks during childhood and elderly. It may present as a primary form with isolated thrombocytopenia or as a secondary form that develops together with immune or infectious disorders. The pathogenesis involves alterations in humoral and cellular immunity, especially the presence of specific antibodies directed against membrane glycoproteins (such as GP IIb/IIIa) play a major role in reducing platelet lifespan [32]. Petechiae, purpura, epistaxis are the most common symptoms. Nevertheless, severe bleeding such as gastrointestinal, intracranial, rectal, and other intra-abdominal hemorrhages may occur in 20.2% of children. First-line therapy for newly diagnosed ITP usually consists of corticosteroids, IVIg at a dosage of 2 g/kg distributed over 2–5 days or a combination of both [33]. According to the American Society of Hematology guidelines, in children with newly diagnosed ITP who have no or minor bleeding, observation, other than IVIg, is strongly recommended [34]. However, the financial burden of IVIg is relevant and, if a reduced dosage could be comparable to the conventional one in terms of clinical efficacy, millions of ITP patients in developing countries would benefit. Different IVIg dose regimens have been investigated during the time but most of the studies are inconclusive. A small, randomized trial highlighted that low-dose IVIg in 2-day regimens of 250, 400, or 500 mg/kg/day in infants and young children with ITP was as effective as 1 g/kg/day (total dose 2 g/kg) in reversing thrombocytopenia and better tolerated [35]. Benesch et al. [35] reported that children who received 0.6 g/kg IVIg achieved a platelet count $>20 \times 10^9$/L within 72 h, without a statistically significant difference to the standard dose. However, the platelet increase was more pronounced in those treated with 2 g/kg which resulted to be more effective in case of high risk to develop bleeding complications [36]. Nuchprayoon et al. studied a medium-high dose IVIg (1 g/kg) in 17 acute ITP in children, with 76% reaching a safe platelet count level of 50×10^9/L within 4 days [37]. A randomized study compared two different dosages of IVIg (0.5 g/kg vs 1 g/kg) in adults with ITP and platelet count $<50 \times 10^9$/l, in preparation for surgery or in a situation with a risk of bleeding. Authors demonstrated that 1 g/kg was more effective due to the higher proportion of responders and the larger daily changes in the platelet count [38]. In 2010, a meta-analysis of 13 randomized controlled trials (RCTs) found that "low-dose IVIg" (< 2 g/kg) was as effective as high-dose IVIg in acute ITP, moreover a lower dosage could prevent side-effects. However, in case of severe bleeding, a high dosage can improve symptoms more quickly and the reasonable treatment protocol must be individualized. This study has flaws that jeopardize the reliability: the low quality of the included trials, most RCTs used 1 g/kg, and the lack of an adequate assessment of a lower dosage [39]. Zhou et al. [40] compared the therapeutic response and clinical outcome of three different IVIg dosages (0.2, 0.3, and 0.4 g/kg/day for 5 days) in adults and children with ITP. They reported similar effectiveness and after a follow-up of three years, they described a comparable risk of developing chronic ITP in both populations. This finding supports the rationale of reducing the financial costs for ITP patients especially for those coming from developing areas that cannot afford the conventional IVIg dose. An important limitation of this study is its non-randomized controlled design, moreover 144 patients were simultaneously treated with glucocorticoids [40]. To our knowledge, the largest study about the efficacy of IVIg for ITP was conducted in 2021. This retrospective study considered real-world data (with a heterogeneous but representative cross-section of the UK ITP patient population) and it stated that one off 1 g/kg IVIg is as effective as two consecutive 1 g/kg doses at a lower cost. The overall response rates were like already published data but collected more detail on platelet counts over time such that the kinetics as well as the degree of response [41].

In conclusion, these results positively show that 1 g/kg IVIg is not only sufficient to manage acute ITP but also has similar effectiveness in preventing chronic ITP. However, in case of severe bleeding the usage of a standard dose guarantees a rapid improvement of symptoms.

2.3. Fetal and neonatal alloimmune thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia is a rare disease that approximately affects one in 1000 births. The consequences may be severe including fetal and neonatal intracranial haemorrhage that can lead to irreversible brain damage or death. The pathogenesis mainly

relies on maternal IgG alloantibodies target paternally inherited human platelet antigens (HPA-1a) on fetal platelets crossing the placenta and causing thrombocytopenia with or without bleeding, in the fetus or the newborn [42]. Pregnancy at risk of fetal and neonatal alloimmune thrombocytopenia are commonly treated with a weekly administration of IVIg at a dose of 1 g/kg (maternal weight) even though this approach is not based on any dose-finding study. Since previous studies reported that placental antibody transfer was not further enhanced with increasing IgG concentrations in the mother, Paridaans et al. [43] hypothesized that a lower dose of IVIg might be as effective as the standard dose. They found that a use of 0.5 g/kg IVIg per week was associated with absence of complications in pregnancies with fetal and neonatal alloimmune thrombocytopenia in women having given birth to an affected sibling without brain bleeds. However, this trial prematurely ended, and it lacked sufficient power to prove the equivalence between the two regimens [43]. A later study on a larger cohort of pregnancies affected by fetal and neonatal alloimmune thrombocytopenia with a previous affected child without intracranial haemorrhage proved that a weekly dose of 0.5 g/kg did not differ to the standard dose in terms of neonatal platelet count or degree of thrombocytopenia [44]. As stated before, the effectiveness of IVIg in pregnant alloimmunized women to prevent intracranial haemorrhage has never been documented in a placebo-controlled clinical trial. Currently, it would be considered unethical to test IVIg's efficacy, since immunoglobulin has been used for this condition for decades. At the opposite of most Western countries, in Norway antenatal IVIg administration is not given in case of HPA-1a alloimmunized pregnancy (low risk) but it is only recommended in case of brain bleeds of the previous child (high risk). A Norwegian retrospective comparative study did not observe any significant difference in neonatal intracranial haemorrhage between immunoglobulin-treated and untreated low-risk pregnancies [42]. This study provides reliable data although the retrospective design and the limited sample size of nontreated pregnancies [42].

In summary, the commitment of plasma for one HPA-1a-alloimmunized pregnant woman is approximately 310 L (a total of 1.4 Kg IgG, considering 1 g/kg/week for 20 weeks and assuming a body weight of 70 kg) which in turns require 4.5 man-month of donor. This huge amount would halve when considering 0.5 g/kg/week, but it remains still unjustified in low-risk pregnancies. Therefore, based on Norway's study, proper risk assessment tools should be developed to start a screening program that would identify pregnant women who would benefit from antenatal IVIg treatment or not. Notably, non-IVIg management does not mean no intervention. When the risk of fetal and neonatal alloimmune thrombocytopenia is recognized before birth several measures are taken including cesarean delivery 1–2 weeks before term and prompt transfusion with compatible platelets to the newborn [42].

2.4. Systemic lupus erythematosus

The use of IVIg in systemic lupus erythematosus (SLE) has been investigated only in small cohorts of patients, hence in-depth knowledge is scarce [45]. A high-dose of IVIg (2 g/kg) monthly remain an off-label indication and it is restricted to refractory cases in which the conventional immunosuppressive options are contraindicated, not well tolerated or as steroid-sparing agents (when disease is controlled only through high-dose steroids) [46]. IVIg has been utilized for different SLE manifestations (haematological, infectious, neurological) but the most widely utilized indication is nephritis [47]. In a single-center, cohort, observational study a standard dose was administered over two to five days in a Latin America subject with SLE. This strategy had a rationale in case of severe SLE manifestations, mainly haematological (including haemolytic anemia and immune thrombocytopenia), concomitant infections and hypogammaglobulinemia [48]. A recent systemic review evaluated the efficacy and safety of IVIg in patients with lupus nephritis refractory to conventional treatment or in case of infections or pregnancies. The standard dose of 2 g/kg monthly was recommended although many studies considered effective a shorter and lower dose of IVIg. The scarcity of high-quality information, the lack of long-term data and the description of variable dosages encouraged new clinical trial to better elucidate the role of IVIg in lupus nephritis [49]. Since the standard regime requires high availability of immunoglobulin, which is not always possible especially in low-income countries, the employment of low-dose IVIg may exert significant benefit for refractory disease at moderate price. Sherer et al. [50] investigated the medical records of 62 SLE patients who received approximately 0.5 g/kg monthly IVIg. They observed clinical improvement in many specific disease manifestations, along with a decrease in SLEDAI score. Nonetheless, thrombocytopenia, alopecia and vasculitis did not improve significantly whereas proteinuria disappeared in only few cases [50]. More recently, Binello et al. [51] reported the clinical case of a woman with a known history of antiphospholipid syndrome, with a fulminant onset SLE. She presented acute renal insufficiency with nephrotic-range proteinuria, central nervous system involvement, severe thrombocytopenia, malar rash, pancreatic injury, and moderate-severe aortic valve steno-insufficiency. She received high dose steroids, which did not exert any effect. Thus, IVIg therapy was delivered at unconventional doses (400 mg/kg for 3 days) due to the multisystem involvement. Remarkably, an unprecedented clinical response was noted 72 h after the first dose [51].

In conclusion, the use of low-dose IVIg in SLE proved to carry out a beneficial effect in subgroups of patients who could not take advantage from the standard of therapy. However, there are still many unanswered questions that deserve more studies, such as the appropriate dosage for selected clinical manifestations and the required duration of the treatment.

3. Low dose IVIg in skin diseases

IVIg treatment has been proposed as a promising therapy in several skin disorders, especially in chronic dermatological inflammation. However, no consensus has been reached about the exact dose to employ to obtain the best results, with the lowest adverse effect, and with the most reasonable costs. IVIg at a dosage of 2 g/kg/month has an immunomodulatory action that exerts effects on phagocytes, complement and circulating autoantibodies, as reported above [52]. On the other hand, there is a lack of information about the efficacy of lower doses of immunoglobulins to treat skin lesions due to various diseases such as toxic epidermal necrolysis (TEN), bullous skin disorders, Darier disease, and dermatomyositis. Here we have the aim to analyze data from literature about the use of low-dose IVIg in these pathological conditions.

3.1. Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN), along with Stevens-Johnson syndrome (SJS), is a rare and severe mucocutaneous reaction, commonly triggered by medications, like antiepileptic drugs (phenytoin sodium, carbamazepine) and antibiotics (cotrimoxazole and ampicillin), characterized by extensive necrosis and detachment of the epidermis. Mucous membranes are affected in over 90% of patients, usually at two or more distinct sites (ocular, oral, and genital) [53]. It can occur in both adults and children. It is characterized by a massive keratinocyte apoptosis, determined by Fas-Fas ligand pathway, resulting in extensive damage of the skin [54,55].

The management of TEN is multidisciplinary and should be driven by a team of clinicians experienced in treating this disease. The main treatment approach for TEN involves removing the causative agent. Supportive care is the cornerstone of management, including wound care, fluid and electrolyte supply, nutritional support, temperature management, pain control, infection prevention and treatment, ocular care, and organ support, if needed [56].

There is no established pharmacologic treatment for TEN. Additional therapies, which reduce inflammation, suppress the immune response,

and provides immunomodulatory effects, such as systemic corticosteroids, IVIg, cyclosporine, plasmapheresis, and anti-tumor necrosis factor (TNF) agents, have been utilized for the treatment of TEN, although it is still unknown which is the most effective one [57].

High dose IVIg was initially proposed as a treatment for TEN based on the hypothesis that Fas ligand (FasL) was the main mediator of widespread keratinocyte apoptosis in TEN and on the finding that high-dose IVIg was able to antagonize FasL effects. However, it is now widely accepted that granulysin, a cytotoxic protein found in cytotoxic T cells, is the most important mediator [58].

The hypothesis behind the efficacy of low-dose IVIg (0.2–0.5 g/kg) in TEN mainly relies on the blockage of Fas-FasL interaction by IVIg, not dependent on their dose. Jagadeesan et al. demonstrated that both children and adult patients treated with a combination of low-dose IVIg, and intravenous dexamethasone (0.1–0.3 mg/kg/day tapered in 1–2 weeks) showed a significantly lower time to arrest the disease progression and to re-epithelize than the group of patients who received the same dose of steroids alone [55].

Mangla's group also used low dose IVIg (0.05–0.1 g/kg/day) for five days in a group of pediatric patients with TEN. The disease stopped progressing in 2.1 days and a complete re-epithelization was observed in 8.3 days. No mortality or side effects were described [54]. In addition, a previous study showed that IVIg treatment with a dose of 0.5–0.75 g/kg/day for four days in children with TEN was safe and effective [59].

3.2. Darier's disease (keratosis follicularis, or dyskeratosis follicularis)

Darier's disease, also known as Darier-White's disease, is a rare autosomal dominant genodermatosis. It is determined by mutations of the ATP2A2 gene, which causes a malfunctioning of the skin barrier. Darier disease is characterized by persistent eruption of numerous scaly, crusted, and itchy bumps primarily found in seborrheic and flexural regions of the body, nail abnormalities, pitting of palms and soles, and mucosal changes [60]. The disease usually starts around puberty and runs a chronic course with exacerbations induced by sun exposure, heat, friction, or infections.

Acantholysis and dyskeratosis are the main histologic features of Darier's disease. Acantholysis is due to the loss of cell adhesion by desmosomes and detachment of keratin filaments from desmosomes, leading to characteristic rounding up of keratinocytes with suprabasal cleft formation. Dyskeratosis is a result of keratinocyte apoptosis and characterized by nuclear condensation and perinuclear keratin clumping. The goals of treatment are the improvement of skin appearance, relief of symptoms (e.g., irritation, pruritus, or malodor), and prevention or treatment of infectious complications. Therapeutic options include antibacterial soaps, antibiotics, antifungals, salicylic acid, retinoids, and topical corticosteroids. Moreover, low-dose IVIg (0.4 g/kg/day every 3 weeks) has been successfully employed in a patient with this disease with a significant improvement of the lesions after four infusions [61]. Furthermore, IVIg at the same dose has been used also in Netherton syndrome, a severe autosomal recessive form of ichthyosis that affects the skin, hair, and immune system. It is characterized by alterations of the skin barrier resulting in chronic inflammation with atopic diathesis and skin infections, especially caused by *Staphylococcus aureus*, which result in flare-ups of the disease. In this case the use of IVIg was supported by the evidence that patients presented a lack of circulating memory B cells and impaired antibody responses [62,63].

3.3. Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are chronic immune-mediated disorders mainly affecting the skeletal muscle. DM is commonly characterized by skin involvement, beside muscular damage. The first line conventional treatment is represented by glucocorticoids, followed by immunosuppressants. IVIg has been shown to be effective in idiopathic inflammatory myopathies (IIM) in patients resistant or only partially response to standard therapy, or in case of severe side effects of conventional treatment [64]. In a randomized controlled trial, Dalakas was the first to publish the effectiveness of IVIg in patients with DM [65].

The precise molecular understanding of how immunoglobulin plays a role in the recovery of inflammatory myopathies has yet to be elucidated. In myositis, environmental factors can trigger the disease in genetically predisposed individuals, by involving various cellular and humoral immunological mechanisms. A first involved pathway is characterized by the presence of cellular infiltrates localized more at the endomysial level, predominantly detected in polymyositis. In dermatomyositis, on the other hand, the immune infiltrate is mostly localized near the microvessels, with capillary leakage and subsequent ischemia. There might be an overlap between these two pathways. Different cellular subsets are involved: T lymphocytes, both CD8+ and CD4+ cells. More recently, the importance of B lymphocytes, macrophages, and dendritic cells that play different roles in dermatomyositis and polymyositis has been described [64]. Kessel et al. [66] was the first to highlight the influence of IVIg on peripheral CD4+ CD25+ T-regulatory cells, enhancing their suppressive function on autoreactive T cells. This aspect was later confirmed by other experts as well.

SCIg could be a valuable alternative to IVIg, however only observational studies and case series have been described so far [66]. It is possible that SCIg may also have an impact on different T cell subpopulations, mainly on T-regulatory cells and/or dendritic cells, thus contributing to the prevention and modulation of autoimmune manifestations and the control of immune homeostasis [67].

Therefore, immunoglobulin has been used off-label as a second- or third-line therapy and has been recommended in European guidelines as a glucocorticoid-sparing agent. Recently, a 16-week randomized, placebo-controlled trial involving patients with active dermatomyositis compared the effects of IVIg at high dose of 2 g/kg vs placebo. The clinical improvement and the overall benefit were greater in the first group, proving, on a large cohort of patients, the known effect of IVIg in leading disease remission [68].

However, a low-dose treatment could be effective as well. Sadayama et al. [68] employed a low-dose scheme (0.1 g/kg/day for 5 days weekly, two courses) accompanied by oral steroid, gradually- tapered, and they observed a complete resolution of skin lesions. It would be worth conducting new studies to confirm these surprising results [69].

3.4. Bullous skin disorders

Autoimmune bullous dermatoses include a collection of antibody-mediated autoimmune diseases characterized by the formation of blisters and erosions on the skin and mucous membranes; pemphigus and bullous pemphigoid are the key examples of this group of diseases [70].

Pemphigus is an autoimmune skin condition caused by IgG autoantibodies that targets desmoglein (Dsg1 and 3), adhesion molecules between cells in desmosomes, leading to acantholysis and intraepidermal blister formation. Pemphigus can be divided into several forms: pemphigus volgaris, foliaceus and paraneoplastic. First-line therapy in the initial phase is represented by systemic corticosteroids (0.5–1.5 mg/kg/d) in combination with immunosuppressive adjuvants, such as azathioprine or mycophenolate mofetil; steroid is gradually tapered in the maintenance phase. In moderate or serious cases, it is possible to employ rituximab (anti-CD20 monoclonal antibody). IVIg at a standard high dose of 2 g/kg/month is a useful therapeutic option for patients who do not reach clinical remission with the first-line treatment [71].

Clinical features like sub-epidermal blisters and erosions on the skin or mucous membranes are typical of pemphigoid diseases, in which autoantibodies are directed against structural proteins of the hemidesmosomes (against NC16A region of BP180). Bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita are forms of this group of diseases. In these diseases systemic corticosteroids are employed firstly too, adding immunosuppressants, plasmapheresis,

IVIg or rituximab when necessary [71].

A case series of four patients with bullous skin disorders (linear IgA disease with bullous lesions, bullous pemphigoid, and pemphigus vulgaris) who received low-dose subcutaneous IgG (20% SCIg-Hizentra; CSL Behring Inc) as adjuvant or maintenance therapy has been recently described [72]. Although IVIg dose for these diseases is 2 g/kg/month, the authors demonstrated the efficacy of a low dose of SCIg (12–40 g/month), with the possibility to reduce the dose over time. This effect is probably determined by a greater stability of serum IgG levels with SCIg, reducing the side effects of a higher dose and limiting the costs.

4. Low-dose IVIg in neurological diseases

IVIg has been demonstrated to be a useful therapeutic tool in several neurological diseases such as myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). It acts through different mechanisms, as explained above, however it seems to have also other actions, not fully understood, which could explain their efficacy on neurologic diseases (e.g., the effects on oligodendroglia and remyelination) [73]. Due to the financial burden and the progressive immunoglobulin shortage, a lower IVIg dosage must be considered. Even though literature is quite scant, in the following paragraphs we report what is known about a lower IVIg dosage in different neurological conditions that guarantees the same effectiveness at a lower cost.

4.1. Chronic neurological conditions

The dose of IVIg employed in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis (MG) and other chronic neurological conditions varies between 0.6 and 2 g/kg administered every 3–8 weeks over one or two days; neurologists usually prefer a maintenance dose of 1 g/kg every 3–6 weeks. Dolezal et al. [73] performed a study on these patients, reducing the IVIg dose from 1 g/kg to a mean dose of 0.67 g/kg (range 0.3–2.5 g/kg) and demonstrating that this is effective on the control of disease (no clinical progression). Moreover, this regimen allowed a 51,4% reduction in the financial expenses, maintaining a good risk/benefit ratio [73].

Also, SCIg could be useful in the chronic treatment of patients with MMN and CIDP, as reported by Hadden and Marreno [74]. They selected patients who were stable under regular long-term IVIg therapy with low treatment doses (<25 g/week) and were interested to switch towards SCIg, when considered appropriate by the neurologists. A major part of the patients showed clinical stability after the switch to SCIg, without needing to increase the dose. The authors did not compare costs of IVIg and SCIg therapy: the first is probably cheaper, however it implies hospital admission and associated costs, whereas the latter determined a greater patient satisfaction, so that it is not evident which is less expensive [74].

IVIg and SCIg have been identified as a successful therapy also in patient with myasthenia gravis regardless of the presence of antibody, as no difference in the main outcome has been observed between seronegative patients or those who presented anti-AchR antibodies. A recent study compared the effects on patients who received IVIg, SCIg or have been subjected to a switch from IVIg or SCIg. The adopted regimen for the IVIg was a loading dose of 2 g/kg followed by 1 g/kg every 3–4 weeks, while the SCIg dose varied from 1 to 1.5 x IVIg dose. Chronic immunoglobulin treatment provided a significant reduction in myasthenia gravis Impairment Index score (main outcome) and a lower use of immunosuppressive drugs. Furthermore, the switch from IVIg to SCIg therapy seemed to determine a longer clinical stability [75]. Several studies demonstrated the efficacy of IVIg also in chronic maintenance therapy, showing clinical improvement even with a low dose [76]. The authors analyzed 52 patients with MG who did not show improvement with pyridostigmine, prednisone, azathioprine, or a combination of these medications; in this group of patients IVIg was considered as a potential maintenance therapy option. IVIg was found to be effective in reducing MG symptoms in this retrospective study, however it was not successful in achieving complete remission or reducing disease activity in these patients.

A following study analyzed a group of patients who received low-dose IVIg (0.4 g/kg every 3–4 weeks after a loading dose of 2 g/kg) to assess the response rate and to determine the features that predict the best responders. Results were encouraging towards the use of chronic low- dose IVIg therapy, as they allow a better clinical outcome, measured as improvement in the Myasthenia Gravis Foundation of America clinical classification. The authors also found that this treatment can be intended as steroid sparing therapy. Both these observations were confirmed after a follow-up period of 36 months [77].

Table 2 summarizes the studies previously reported about low-dose IVIg in different clinical conditions.

5. Conclusion

Following the hypothesis of Paul Imbach about the ability of IVIg to modulate the immune system in multiple synergistic ways, several studies have been conducting during the time proving that both IVIg and SCIg are effective in multiple autoimmune diseases. In such conditions IVIg are usually administered during the acute phase at the dosage of 2 g/kg which is considered high-dose. SCIg might be helpful as a maintenance therapy. Since the kinetics and distribution of SCIg are different from those given intravenously, it is conceivable that SCIg acts at different levels. It is thus possible that the very high serum IgG peaks could be relevant for the acute phase of the immune reaction, whereas serum IgG steady state levels obtained with SCIg have an impact on chronic mechanism of damage. High-dose IVIg (2 g/kg monthly) given intravenously affects mostly the “humoral” component of the immune response, being more indicated in acute situations that need a prompt action, such as low platelets count in immune thrombocytopenia [67]. On the contrary, a lower dosage (i.e., ≤1 g/kg monthly) given by the subcutaneous route, could act on the “cellular” component, thus affecting the response of T or other cells such as dendritic cells. In this case the onset of action can be delayed but prolonged in time. It is difficult to understand which mechanisms of IVIg/SCIg are prevalent in one disease compared to another. Therefore, by modifying the dose and/or the modality of administration of immunoglobulin, it could be possible to interfere with different pathways of the immune system and to exert a beneficial/favorable immunomodulation in immune-mediated diseases [67].

Although IVIg products are generally considered safe and effective, mild adverse reactions might be observed in approximately 25% of the treated patients, mostly due to excessive infusion rate and high IgG levels achieved after therapy. Furthermore, immunoglobulin has certain inherent limitations including dependence on a broad plasma donor pool and the large doses of product (up to 2 g/kg body weight) needed for therapy.

These challenges may potentially be addressed, for example, by reducing the minimum effective dosage, by optimizing the dosage on the ideal weight and not on the real one or even by lengthening the interval between doses [9,23]. Moreover, due to the immunoglobulin's shortage, for patients who require IVIg long-term treatment after the first three months, some experts believe necessary a reassessment of the clinical manifestations to decide whether to continue or not with the immunomodulatory treatment and, if yes, at which dose. In these cases, it is reasonable first to consider a reduction of the IVIg dosage (e.g., 1 g/kg per month) and then increasing the interval time between one treatment and the following one (a cycle three times every two months and thereafter two times every three months) [20]. Notably, in chronic conditions that require chronic intravenous therapies (e.g., IVIg), the “stability status” expressed as “non-worsening status” attributed to

Table 2
Previous studies reporting the usage of low-dose IVIg in different clinical conditions.

Reference	*Study Design*	*Main Results*
KAWASAKI DISEASE		
Sakata et al., 2007	Randomized prospective study. Group A (n = 54): 2 g/kg and Group B (n = 55): 1 g/kg. In case of resistance additional IVIg: A2 (n = 50/54) tot 2 g/kg A4 (n = 5/54) tot 4 g/kg B1 (n = 23/55) tot 1 g/kg B2 (n = 26/55) tot 2 g/kg B4 (n = 6/55) tot 4 g/kg	No significant difference was observed in the number of coronary aneurysms between the two protocol groups (p = 0.176).
Yeo and Choi, 2010	Retrospective clinical study. Group A (n = 220): 1 g/kg vs Group B (n = 54): 1 g/kg twice or more	A single infusion of medium-dose immunoglobulin was effective in 80% of patients with KD
He et al., 2021	Multicenter, open-label, blind-endpoint randomized controlled trial. Group A (n = 138): 2 g/kg x 1 Group B (n = 127): 1 g/kg x 2 Group C (n = 132): 1 g/kg x1 In case of resistance, a second dose IVIg (2 g/kg) was given. There was no significant difference in the incidence of initial IVIg resistance (P = 0.364).	No difference was found in the outcomes: hour to defervescence after completion of initial IVIg, in the incidence of coronary artery lesions, changes of laboratory data, total fever days, and length of stay. Group C patients had the lowest total dose of IVIg (mean: 1.2 vs 2.2 vs 2.1 g/kg; $P < 0.001$) and hospitalization expenses (mean: 8443.8 vs 10,798.4 vs 11,011.4 Chinese Yuan; P < 0.001) than other two groups.
Suzuki et al., 2020	Retrospective, nationwide observational study. Group A (n = 1134): 2 g/kg vs Group B (n = 198): 1 g/kg 4:1 propensity score matching Group A (n = 788): 2 g/kg vs Group B (n = 197): 1 g/kg	In the propensity score-matched groups there were no significant differences in the proportions of coronary artery lesions (p = 0.587), IVIg resistance (p = 0.054), and length of stay (p = 0.476). Medical costs were significantly higher in the high-dose group than in the low-dose group ($p < 0.001$). Adverse events: 1 patient (2 g/kg) had acute coronary syndrome. Hyper-viscosity syndrome was not diagnosed
IMMUNE TROMBOCYTOPENIA (ITP)		
Warrier et al., 1997	2 prospective, multicenter, randomized, open-label, and parallel studies (in children). Study 1: (n = 6) 400 mg/kg for 2 days; (n = 6) 1 g/kg for 2 days Study 2: (n = 6) 250 mg/kg for 2 days; (n = 6) 500 mg/kg for 2 days	In the low-dose group thrombocytopenia reversed just as effectively as in the high-dose group (1 g/kg) Adverse events varied by dosage group, but the difference was not significant (p = 0.57). Anaphylactoid reaction occurred in one patient (400 mg/kg) Aseptic meningitis in one patient (1 g/kg)
Benesch et al., 2003	Prospective, randomized single-center trial (in children). Group A (n = 17): 1 g/kg for 2 days vs Group B (n = 17): 0.3 g/kg for 2 days	Although the PLT count >20 $\times 10^9$ was achieved by both groups, the increase in group A was faster. Higher dosages are more effective if PLT count is very low
Nuchprayoon et al., 2001	Prospective study (in children). (n = 17) treated with 1 g/kg. Within 4 days: 13 recovered (PLT $\geq$ 50,000), 4 needed a second dose.	In ITP, an initial dose of 1 g/kg IVIg may be used. If inadequate response is observed (platelet count not reaching 30,000) by 48 h, another dose of 1 g/kg may be

Table 2 (*continued*)

Reference	*Study Design*	*Main Results*
	During the weekly follow-up, 2 needed IVIg retreatment	repeated. Adverse events: one patient had a transient macular rash
Godeau et al., 1999	Randomized trial (in adults) Group A (n = 19) 0.5 g/kg ➔ at day 4 (n = 13) non responders received additional 1.5 g/kg Group B (n = 18) 1 g/kg ➔ at day 4 (n = 6) non responders received additional 1 g/kg	In adults, higher dosages were more effective: higher proportion of responders and larger daily changes. Infusion of a low dose IVIg did not jeopardize the efficacy of IVIg reinfusion
Qin et al., 2010	Meta-analysis of 13 randomized controlled trials comparing high-dose (2 g/kg) vs low-dose ($\leq$ 2 g/kg)	No statistically significant differences in time of cessation of bleeding (p = 0.94), time of platelet count beginning to rise (p = 0.71) and time of platelet to reach peak (0.69). High-dose regimens improve symptoms of severe bleeding more quickly. Low-dose had a significant reduced risk of side effects odds ratio ((OR) 0.39 [95% confidence interval (CI) 0.180.83] p = 0.01)
Zhou et al., 2016	Prospective study Group A (n = 63) 0.2 g/kg/day Group B (n = 63) 0.3 g/kg/day Group C (n = 41) 0.4 g/kg/day IVIg was administered until PLT count mounted to 50 $\times$ 10^9/L or after 5 days (regardless PLT amount)	No statistically significant difference in therapeutic response (p = 0.459), mean time for PLT to raise to 30 $\times$ 109/L, clinical outcome after 3 years
HaemSTAR Collaborators, 2022	Retrospective study Comparison between 1 g/kg off and 1 g/kg for two consecutive infusions	No significant differences in the speed or duration of PLT response. 1 g/kg is effective, less expensive, better use of a scarce resource with reduced side-effects
FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (FNAIT)		
Paridaans et al., 2015	Randomized trial Group A (n = 12): 0.5 g/kg/week Group B (n = 11): 1 g/kg/week	Despite the lack of sufficient power to prove equivalence between the two protocols, the dose of 0.5 g/kg weekly appears safe and effective for pregnancies complicated by FNAIT in women with an affected sibling without ICH
Kamphuis et al., 2016	Cohort study Group A (n = 46): 0.5 g/kg/week Group B (n = 63): 1 g/kg/week	No difference in PLT count at birth and incidence of severe thrombocytopenia
SYSTEMIC LUPUS ERYTHEMATOSUS		
Sherer et al., 2008	Retrospective study 62 cases who received approximately 0.5 g/kg	Clinical improvement for many manifestations along with SLEDAI score. Only thrombocytopenia, alopecia and vasculitis did not improve
Binello et al., 2018	Case report IVIg dose 1.2 g/kg (400 mg/kg/3 days)	IVIg might constitute a valuable therapeutic modality as a last-resort strategy in cases of fulminant SLE
TOXIC EPIDERMAL NECROLYSIS		
Jagadeesan et al.,2013	Prospective open labeled study 36 patients divided into two groups. Group A (n = 18) IVIg dose (0.2–0.5 g/kg in 3 days) and systemic steroids (intravenous dexamethasone	A statistically significant difference was observed between the two groups in the time taken for arrest of disease progression, and for epithelization. No side effects

(*continued on next page*)

Table 2 (*continued*)

Reference	*Study Design*	*Main Results*
	reduced within 1–2 weeks according to response) Group B ($n = 18$) only dexamethasone as in Group A	
Mangla et al., 2005	Open uncontrolled study 10 TEN pediatric patients treated with IVIg (0.05–0.1 g/kg/day) along with antibiotics and supportive care	IVIg demonstrated to be a useful and safe treatment for children with TEN (no mortality, no side effects)
Tristani-Firouzi et al., 2002	Retrospective analysis Group A ($n = 8$) TEN pediatric patients (June 1999–March 2001): IVIg, 0.5 to 0.75 g/kg/ day for 4 consecutive days Group B (n = 3) pediatric patients (historical controls, 1988–1998) with TEN not treated with IVIg who received plasmapheresis and fresh-frozen plasma	Group A: lower average length of hospitalization, average time to arrest in progression of lesions and to complete re-epithelialization than group B. Statical analysis not possible for the small number of patients and because group B received also fresh-frozen plasma (mechanism like IVIg)
DARIER DISEASE		
Legrand et al., 2020	Case report 1 patient treated with IVIg (0.4 g/kg every 3 weeks)	Clinical improvement after 4 infusions; sustained clinical response with a maintenance therapy every 3 weeks for 2 years follow-up
DERMATOMYOSITIS		
Sadayama et al., 1999	Case report IVlg therapy (0.1 g/kg/day for 5 days weekly, 2 courses).	Resolution of cutaneous manifestations after the second course of IVIg
BULLOUS SKIN DISORDERS		
Streu et al., 2020	Case report 4 patients with bullous skin disorders refractory to several immunosuppressant treatment received a low-dose of SCIg (12–40 g/month) as adjuvant or maintenance therapy 1) IgA linear disease; 2) Bullous pemphigoid; 3) Bullous pemphigoid pemphigus vulgaris	Clinical remission with the possibility to reduce the dose over time
NEUROLOGICAL DISEASES		
Dolezal et al., 2014	Observational study 26 patients with several neurological diseases received a maintenance dose of 1 g/kg every 4 weeks. CIDP n = 13 MMN $n = 4$ MG n = 3 Stiff-person syndrome $n = 1$ Paraprotein associated neuropathy n = 1 Paraneoplastic neuropathy $n = 4$ CIDP = Chronic inflammatory demyelinating polyneuropathy MG = Myasthenia gravis MMN = multifocal motor neuropathy	The dose of IVIg was reduced to a mean dose of 0.67 g/kg (range 0.3–2.5 g/kg) in 12 months; during the follow-up phase further reduction of the dose to 0.60 g/kg
Hadden et al., 2015	Nonrandomized, partially prospective, observational study 8 patients (MMN n = 4; CIDP n = 4) on low-dose IVIg (<25 g/week) (hospital administration), switched to SCIg (home administration)	7 patients were stable, 6 with a SCIg dose like the IVIg, while the other needed to increase. Greater satisfaction with SCIg therapy
Alcantara et al., 2021	Retrospective study 34 patients with generalized MG treated with chronic Ig therapy (IVIg/SCIg $n = 30$; SCIg $n = 3$; IVIg n = 1)	Significant reduction in MGII *(Myasthenia Gravis Impairment Index)* score, pyridostigmine and immunosuppressants use
Hellmann et al., 2014	Retrospective study 52 patients with MG refractory to pyridostigmine, prednisone, azathioprine received chronic IVIg therapy (loading dose 2 g/kg; maintenance dose 0.4 g/kg every 3–6 weeks)	IVIg therapy reduced symptoms of MG, but not to achieve full remission or significantly decrease disease activity.
Wilf-Yarkoni et al., 2021	Retrospective study 109 patients with MG treated with IVIG (loading dose of 2 g/kg over 5 days; maintenance dose of 0.4 g/Kg every 3–4 weeks)	Clinical improvement: at least one-point more in the MGFA scale for 61.4% of patients. Extended steroid-sparing effect and clinical stability (36 months follow- up) *MGFA = Myasthenia Gravis Foundation of America*

monthly infusion is not properly related to IVIg but rather is a conditioning effect, a biopsychosocial model based on learned response and expectation, that collectively account for a placebo/nocebo phenomenon. Especially for neurological conditions, when IVIg therapy is reduced in dose or the intervals are prolonged, a 40% of patients express subjective symptoms although their neurological assessment remain unchanged. This is a combination of conditioning, fear, effects of various psychological, environmental, emotional, or aging factors and uncertainties of present life events that collectively built the conviction that monthly IVIg ensures stability. To face this problem clinicians should converse with their patients, continue the therapy for 3 months and if no objective benefit is observed to stop it. If there is a certain benefit, as previously states, the dose should be reduced, the intervals prolonged, and periodic dependency tests are needed to objectively prove a disease worsening [20].

In conclusion, since immunoglobulin's shortage is a world-wide problem and the costs to obtain a highly purified product are increasing, more standardized and high-quality studies are needed to find out if a lower dose than the standard 2/kg/monthly may exert a sufficient immunomodulatory role to control the diseases.

MGD and YS were responsible for the study's conception and design. EA, SA, and EB reviewed the literature studies and wrote the first draft. All Authors contributed to analyses of the references. MGD and YS revised the manuscript critically for intellectual content. All authors gave their final approval of the version of the manuscript to be published.

Disclosure

Authors declare that they do not use generative AI and AI-assisted technologies in the writing process of this manuscript.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Data will be made available on request.

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